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Commentary

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Limited recovery following acellular nerve allograft reconstruction in major peripheral nerve injuries

David Chi, Anna Rose Johnson, Susan E. Mackinnon

Division of Plastic and Reconstructive Surgery, Department of Surgery, Washington University School of Medicine, Saint Louis, MO 63110, USA.

Correspondence to: Prof. Susan E. Mackinnon, Division of Plastic and Reconstructive Surgery, Washington University School of Medicine, Campus Box 8238, 660 South Euclid Avenue, St. Louis, MO 63110, USA. E-mail: mackinnons@wustl.edu

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Abstract

Recent studies suggest that acellular nerve allografts (ANA) have similar efficacy as nerve autografts in certain applications of nerve surgery. However, multiple studies also demonstrate the limitations of nerve allografts, resulting in poor patient outcomes. This submission discusses a recent case series of patients who failed allograft use with subsequent histologic analyses of these allografts. Recommendations on the treatment of nerve gaps are presented, drawing from our current understanding of allograft and autograft utility in reconstruction. Factors taken into account include recipient critical nerve function, existent nerve gap, and nerve diameter.

Keywords: Nerve reconstruction, peripheral nerve, acellular nerve allograft, nerve autograft

The increasing use of acellular nerve allografts, nerve conduits, and nerve wraps in nerve reconstruction provides a potential new alternative to nerve repair and nerve autograft. Recent studies, most supported by industry, suggest that outcomes may be comparable between autografts and acellular nerve allografts (ANA)[1,2]. However, a large study from Switzerland showed that ANA reconstruction resulted in poorer outcomes when used to reconstruct longer length motor nerve injuries. Specific details regarding individual use cases are often uncaptured in large cohorts, and more nuance is required to accurately interpret and implement these findings into clinical practice.

In a study by Peters *et al.*, a special cohort of patients offered the rare clinical opportunity where the failed allograft was close enough to the nerve end-target to justify a simultaneous acellular nerve allograft excision and autograft reconstruction[3]. Histologic analyses in these patients demonstrated the presence of myelinated axons proximal to the allograft and a paucity of regenerating axons through the allograft[3]. Figure 1 includes a gross image with corresponding histologic sections demonstrating the presence of myelinated axons proximal to, within, and distal to the ANA. For proximal nerve injuries, the time and distance to end target are usually too long and are thereby prohibitive of autograft reconstruction. The failed ANA is then frequently left in place as the senescent axons traveling through the allograft have dwindled and are thus useful for pain control while distal nerve transfers are performed[4,5].

Nerve autografts have been considered the gold standard, with the cellular and extracellular components serving as a biologic scaffold to guide axonal regeneration. However, there are limits to autograft efficacy as dictated by nerve gap length and diameter. For example, 6 cm appears to be a useful approximate ceiling for what outcomes may be expected in reconstructing motor nerve gaps, as demonstrated in a study assessing outcomes from common peroneal nerve decompression and reconstruction[6-8]. However, in another study, gaps greater than 5 cm were associated with 10% meaningful motor recovery and 52.9% meaningful sensory recovery[9]. Additionally, large diameter nerve gaps represent a greater challenge to revascularization demand for autografts and acellular nerve allografts. Increasing nerve diameter increases central necrosis during the period of nerve recovery. In a study by Leckenby *et al.*, ANA nerve diameters greater than 3 mm were inhibitory to axonal growth[9]. Autografts revascularize via longitudinal inosculation, while acellular nerve allografts require the reconstitution of entirely vascular networks *de novo*[10,11]. Hence, even with matched diameters, allografts have been demonstrated to take several times longer than autografts to revascularize[12].

Fortunately, for shorter or smaller-diameter nerve gaps, acellular nerve allografts and nerve conduits may return function to some degree since only 25%-30% of nerve fibers are necessary, given the compensatory expansion of motor and sensory units[13,14]. However, when critical functions are being restored, it would be reasonable to utilize "gold standard" autografts to maximize functional recovery. In one of the few studies not funded by industry, meaningful motor recovery after ANA declined notably with diameters exceeding 2 mm and lengths of 2 cm[9]. Utilizing an off-the-shelf allograft is less time-consuming than harvesting an autograft, but in keeping with the principles of reconstructive surgery, the solution must match the demands and functional importance of the defect. For example, cortical bone allografts certainly have their place in skeletal reconstruction; however, when bone gap distance and weight-bearing criteria are considered, vascularized bone flaps may be the suitable treatment[15,16]. Therefore, in modern nerve surgery, it remains the practice of the senior author to treat critical motor and sensory nerves with nerve autograft. By contrast, acellular nerve allografts are utilized for noncritical or small-diameter sensory nerves and to prevent neuroma formation by utilizing the dwindling regeneration that occurs over a long distance[17].

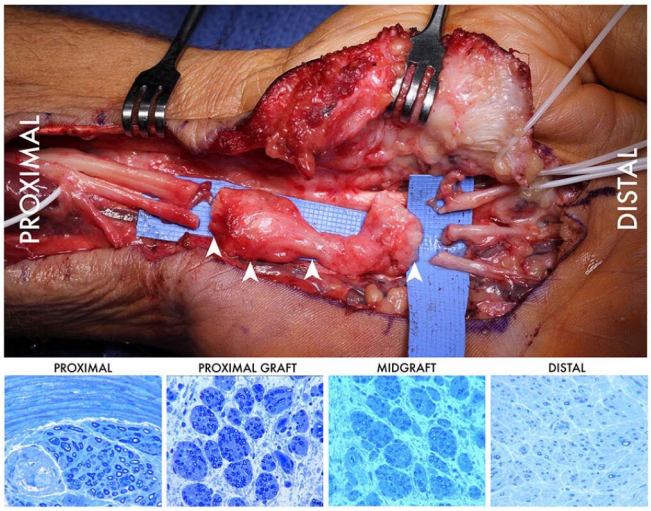

Figure 1. Patient 1 with intraoperative findings demonstrating a large proximal neuroma of the median nerve and an 8-cm nerve gap present upon resection of the allograft. The arrows demonstrate the location of the histological sections. Note the abundance of myelinated axons in the median nerve proximal to the coaptation site of the proximal median nerve and the allograft. Note the decrease of myelinated axons across the allograft, as myelinated axons are visible within the midgraft, but only a few myelinated axons present within the distal nerve.

DECLARATIONS

Authors' contributions

Made substantial contributions to manuscript conception, manuscript development, and manuscript editing: Chi D, Johnson AR, Mackinnon SE

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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